PATENT COOPERATION TREAT .

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 August 1997 (07.08.97)	
International application No. PCT/GB96/03221	**Applicant's or agent's file reference** N.70283A
International filing date (day/month/year) 23 December 1996 (23.12.96)	**Priority date** (day/month/year) 21 December 1995 (21.12.95)
Applicant HERMON-TAYLOR, John et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

21 July 1997 (21.07.97)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Aino Metcalfe
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992) 1625555

PATENT COOPERATION TREA

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COMMUNICATION OF
INTERNATIONAL APPLICATIONS

(PCT Article 20)

To:

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Date of mailing:
12 September 1997 (12.09.97)

The International Bureau transmits herewith copies of the international applications having the following international application numbers and international publication numbers:

International application no.:	International publication no.:
PCT/GB96/03221	WO97/23624

CORRECTED VERSION
VERSION CORRIGEE

The International Bureau of WIPO
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1211 Geneva 20, Switzerland

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1669972

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
N.70283A		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB96/03221	23/12/1996	21/12/1995
International Patent Classification (IPC) or national classification and IPC		
C12N15/31		
Applicant		
ST GEORGE'S HOSPITAL MEDICAL SCHOOL et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☐	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/07/1997	16.03.98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Sprinks, M Telephone No. (+49-89) 2399-8706

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB96/03221

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-56 as originally filed

Claims, No.:

1-23 as received on 22/12/1997 with letter of 22/12/1997

Drawings, sheets:

1/1 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☒ the entire international application.

☐ claims Nos. .

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

III) Non-establishment of opinion

Clarity

1) Because the subject-matter of **claims 1-23** and the parts of the description relating to them are so unclear, a meaningful assessment of novelty/inventive step could not be made. The reasons are given below.

2) Although the application discloses nucleotide and polypeptide sequences corresponding to open reading frames (ORFs) which are part of or homologous to cloned sequences within a pathogenicity island (GS) of Mycobacterium avium and Mycobacterium paratuberculosis, it provides no evidence of the expression of the putatively encoded polypeptides or their biological/immunological role.

   For nucleotide and peptide sequences whose function, expression and, in the latter case, very existance is based purely upon surmise, examination with respect to novelty, inventive step and industrial application cannot be carried out, since it is impossible to determine upon what subject-matter and using what criteria such examination could be based.

3) Furthermore, there is no special technical feature which links the nucleotides and polypeptides referred to in the present claims. Consequently, every sequence claimed represents a separate "invention" and the application does not comply with the requirements of unity (Rules 13.1-13.3 PCT) or clarity (Article 6 PCT), since every optional sequence within each claim must be treated independently such that the number of independent claims is excessive and the claims as a whole are unclear.

   Although the numerous polynucleotides (ORFs) referred to in the claims might be regarded as "fragments" of a new gene complex and therefore "useful" as probes to detect it, the technical relationship between them does not involve one or more of the same or corresponding technical features (sequences) since they all correspond to (or recognise) different genes of unknown function (this is also true of expressed sequence tags which are "fragments" of a larger gene complex - a whole organism).

The position of these genes within a complex is (as far as unity is concerned) irrelevant, particularly when it appears that said complex only provides a technical effect if all the genes are present in combination. If the only known contribution which a set of genes, considered as a whole, makes over the prior art is the technical effect resulting from their combined presence in an organism, then only their use in combination (or the complex as a whole) should be claimed in a single application, and not the individual genes themselves (whose individual technical effects are not only unknown but probably quite diverse). Similar arguments would apply to proteins and antibodies.

The fact that several structurally and/or functionally disparate products may be used for the same ultimate purpose (e.g. detecting a particular gene complex or genome) does not unify the products *per se* - there must be a direct technical relationship between them.

CLAIMS

1. A polypeptide in substantially isolated form which comprises a sequence selected from the sequences of Seq.ID.No: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 29, or a polypeptide substantially homologous thereto.

2. A polypeptide in substantially isolated form which comprises a sequence selected from the sequences of Seq.ID.No: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 and 29.

3. A polypeptide which comprises a fragment of a polypeptide defined in claim 1 or 2, said fragment comprising at least 12 amino acids and an epitope.

4. A polynucleotide in substantially isolated form which encodes a polypeptide according to any one of claims 1 to 3.

5. A polynucleotide in substantially isolated form which is capable of selectively hybridizing to Seq.ID.No: 3 or 4 or a fragment thereof.

6. A polynucleotide fragment according to claim 5 which comprises a sequence selected from the sequences of Seq.ID.No: 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27, or a polynucleotide at least 90% homologous thereto.

7. A polynucleotide in substantially isolated form comprising a sequence selected from the sequences of Seq.ID.No: 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27.

8. A polynucleotide probe which comprises a fragment of at least 15 nucleotides of a polynucleotide as defined in any one of claims 4 to 7, optionally carrying a revealing label.

9. A recombinant vector carrying a polynucleotide as defined in any one of claims 4 to 7.

10. An antibody capable of binding a polypeptide or fragment thereof as defined in any one of claims 1 to 3.

11. An antibody capable of binding a polypeptide or fragment thereof wherein the polypeptide is a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or is a peptide substantially homogolous thereto.

12. A test kit for detecting the presence or absence of a pathogenic mycobacterium in a sample which comprises a polynucleotide according to any one of claims 4 to 8, a polypeptide according to any one of claims 1 to 3, a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto, or an antibody according to, any one of claims 10 or 11.

13. A method of detecting the presence or absence of antibodies in an animal or human, against a pathogenic mycobacteria in a sample which comprises:

(a) providing a polypeptide according to any one of claims 1 to 3 or a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto, which comprises an epitope;

(b) incubating a biological sample with said polypeptide under conditions which allow for the formation of an antibody-antigen complex; and

(c) determining whether antibody-antigen complex comprising said polypeptide is formed.

14. A method of detecting the presence or absence of a polypeptide according to any one of claims 1 to 3 or a polypeptide which comprises a sequence selected from the

sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto in a biological sample which method which comprises:

(a) providing an antibody according to any one of claims 10 and 11;

(b) incubating a biological sample with said antibody under conditions which allow for the formation of an antibody-antigen complex; and

(c) determining whether antibody-antigen complex comprising said antibody is formed.

15. A method of detecting the presence or absence of cell mediated immune reactivity in an animal or human, to a polypeptide according to claims 1 to 3 or a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto, which method comprises

(a) providing a polypeptide according to any one of claims 1 to 3 or a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto, which comprises an epitope;

(b) incubating a cell sample with said polypeptide under conditions which allow for a cellular immune response such as release of cytokines or other mediator or reaction to occur; and

(c) detecting the presence of said cytokine or mediator or cellular response in the incubate.

16. A pharmaceutical composition comprising a polypeptide according to any one of claims 1 to 3 in a suitable carrier or diluent.

17. A composition according to claim 16 or a composition comprising a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto,

for use in the treatment or prevention of diseases caused by mycobacteria.

18. A method of treating or preventing mycobacterial disease in an animal or human caused by mycobacteria which express a polypeptide according to claims 1 to 3 or a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto, which method comprises vaccinating or treating an animal or human with an effective amount of said polypeptide.

19. A method of treating or preventing mycobacterial diseases in animals or humans caused by mycobacteria containing the polynucleotide of Seq.ID.No: 3 or 4, which method comprises vaccinating or treating an animal or human with an effective amount of a polynucleotide according to claims 4 to 7, a vector according to claim 9 or a polynucleotide which encodes a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto.

20. A method according to claims 18 or 19 for increasing the in vivo susceptibility of mycobacteria to antimicrobial drugs.

21. A normally pathogenic mycobacterium, whose pathogenicity is mediated in all or in part by the presence or the expression of a polypeptide as defined in any one of claims 1 to 3 or a polypeptide which comprises a sequence selected from the sequences of Seq.ID.No: 31, 33, 35, 37 and 39 or a polypeptide substantially homogolous thereto, which mycobacterium harbours an attenuating mutation in a gene encoding one of the said polypeptides.

22. A vaccine comprising a mycobacterium as claimed in claim 21.

23. A vaccine according to claim 22 wherein the mycobacteria is selected from *Mavs*, *Mptb* and *Mtb*.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/31, C07K 14/35, C12N 15/70, C07K 16/12, C12Q 1/68, G01N 33/569, 33/68, A61K 39/04, 48/00

A3

(11) International Publication Number: **WO 97/23624**

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9526178.0 21 December 1995 (21.12.95) GB

(71) Applicant *(for all designated States except US)*: ST. GEORGE'S HOSPITAL MEDICAL SCHOOL [GB/GB]; Cranmer Terrace, London SW17 0RE (GB).

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(74) Agents: GOLDIN, Douglas, Michael et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States: AU, CA, JP, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(88) Date of publication of the international search report:
12 September 1997 (12.09.97)

(54) Title: POLYNUCLEOTIDES AND POLYPEPTIDES IN PATHOGENIC MYCOBACTERIA AND THEIR USE AS DIAGNOSTICS, VACCINES AND TARGETS FOR CHEMOTHERAPY

(57) Abstract

The invention provides a nucleotide sequence representing a pathogenicity island found in species of pathogenic mycobacteria. The islands are shown as SEQ ID NOs: 3 and 4 and comprises several open reading frames encoding polypeptides. These polypeptides and their use in diagnosis and therapy form a further aspect of the invention.

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INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 96/03221

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/31 C07K14/35 C12N15/70 C07K16/12 C12Q1/68
G01N33/569 G01N33/68 A61K39/04 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K C12Q G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database EMBL, Entry MT024, Accession number U00024, 5.Jan.1995 nt.15203-15934 100% homology with SeqID:36 nt.14306-15133 100% homology with SeqID:38 XP002033471 cited in the application	1-5,8-11
Y		12-23
A		6

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 1997	03.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Macchia, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Database EMBL, Entry MTCY277, Accession number Z79701, 18.Sep.1996 nt.34705-35493 100% homology with SeqID:30 nt.31972-32994 100% homology with SeqID:32 nt.33956-34687 100% homology with SeqID:34 XP002033472 cited in the application	1-5,8-11
A	---	6
P,X	Database EMBL, Entry MTAD1, Accession number AD000001, 15.Dec.1996 nt.6775-7562 100% homology with Seq.ID:30 nt.9273-10295 100% homology with Seq.ID:32 nt.7580-8311 100% homology with Seq.ID:34 XP002033473	1-5,8-11
A	---	6
P,X	Database EMBL, Entry MTCY349, Accession number Z83018, 26.Nov.1996 nt.34695-35426 100% homology with SeqID:36 nt.33797-34624 100% homology with SeqID:38 XP002033474	1-5,8-11
A	---	6
P,X	Database EMBL, Entry MTAD9, Accession number AD000009, 15.Dec.1996 nt.15203-15934 100% homology with SeqID:36 nt.14306-15133 100% homology with SeqID:38 XP002033475	1-5,8-11
A	---	6
Y	WO 95 01441 A (STATENS SERUMSINSTITUT ;ANDERSEN PETER (DK); ANDERSEN AASE BENGAAR) 12 January 1995 see page 3, line 20-23 see page 4, line 28-34 see page 21, line 7 - page 23, line 17 see page 25, line 1-29 see claims 1,15-17,29-32,34,47,48	12-20
Y	---	20
	VACCINE, vol. 12, no. 16, 1994, pages 1537-1540, XP002026338 LOWRIE D B ET AL: "TOWARDS A DNA VACCINE AGAINST TUBERCULOSIS" see page 1537 - page 1538	

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INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/GB 96/03221

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 26312 A (JACOBS WILLIAM R JR ;COLLINS DESMOND MICHAEL (NZ); BANERJEE ASESH) 24 November 1994 see abstract see page 19, line 6-15 see page 40; claim 18 ---	21-23
A	NATURE, vol. 351, no. 6326, 6 June 1991, pages 456-460, XP000605495 STOVER C K ET AL: "NEW USE OF BCG FOR RECOMBINANT VACCINES" see page 456 - page 457 -----	22,23

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I national application No.
PCT/GB 96/03221

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19,20,21
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 19,20,21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...nal Application No
PCT/GB 96/03221

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9501441 A	12-01-95	AU 7068894 A	24-01-95
		CA 2165949 A	12-01-95
		EP 0706571 A	17-04-96
WO 9426312 A	24-11-94	AU 6912194 A	12-12-94
		AU 6949694 A	12-12-94
		EP 0707496 A	24-04-96
		JP 9501823 T	25-02-97
		WO 9426765 A	24-11-94